REMARKS/ARGUMENTS

Prior to entry of this amendment, claims 1-3, 5-12, 14-25, 27-41 and 44-46 were pending. Claims 9-12, 14-19 and 20 are canceled without prejudice herein. Claims 21, 22, 25, 37-39, 44 and 45 are amended for clarity. Applicants submit that no new matter is introduced by way of the amendment. Applicants expressly reserve the right to pursue the subject matter of any canceled claims in subsequent continuation, divisional or continuation-in-part applications. The specification has been amended to remove disclosure previously added by way of amendment.

Specification

The amendment filed March 19, 2004 is objected to under 35 U.S.C. 132 because it allegedly introduces new mater into the disclosure. Without necessarily agreeing with the propriety of the objection, but rather to expedite prosecution of this case, Applicants have amended the specification to remove the language previously submitted by way of the amendment. Applicants request acknowledgement that the objection is withdrawn.

Claim Rejections Under 35 U.S.C. §112, First Paragraph

Claims 9, 19, 25, 37 and 45 stand rejected under 35 U.S.C. 112, first paragraph for allegedly failing to comply with the written description requirement. Without necessarily agreeing with the propriety of the rejection, Applicants have canceled claims 9 and 19. Claims 25, 37 and 45 have been amended to delete reference to phosphorothioate. As such, the rejection is moot. Applicants expressly reserve the right to pursue any subject matter of canceled or amended claims in subsequent continuations, divisionals or continuations-in-part. Applicants respectfully request the Examiner to withdraw the rejection.

Claim Rejections Under 35 U.S.C. §102

Claims 1, 2, 5, 6, 10-12, 14-16, 21, 22, 27-34 and 46 stand rejected under 35 U.S.C.

102(b) as being anticipated by Shi et al. (PCR Meth. Appl., vol. 3, pp. 46-53, 1993). Applicants respectfully traverse the rejection. Moreover, the rejection of claims 10-12 and 14-16 is moot because the claims are canceled, without prejudice herein.

Anticipation requires that each and every element of a claim is described in a single prior art reference, either expressly or inherently. *See* MPEP 2131 *citing Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). "The identical invention must be shown in as complete detail as is contained in the ... claim." *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989). Furthermore, the elements must be arranged as required by the claim. *In re Bond*, 910 F.2d 831, 15 USPQ2d 1566 (Fed. Cir. 1990).

Shi discloses a PCR based method for constructing a gene. Specifically, Shi teaches a method for constructing Lym-1 antibody variable regions. The method of Shi includes providing several PCR primers that overlap with either an upstream target sequence, a downstream target sequence, or with each other, amplifying to extend overlapping templates and primers and performing a final PCR step to amplify the full length sequence.

In contrast, claim 1 requires a method that includes performing a first amplification step to amplify a first target fragment of DNA with a first primer pair, wherein the first primer pair, upon such amplification, adds to *first and second ends of the first fragment predetermined first and second regions of complementarity to form a second DNA fragment having said first region of complementarity at a first end and a second region of complementarity at a second end of said second DNA fragment*. The claim further requires, *inter alia*, providing a promoter-containing sequence and a terminator-containing sequence, said promoter-containing sequence further including a region complementary to said first region of complementarity and said terminator-containing sequence including a region complementary to said second region of complementarity. Thus, the claim requires adding to first and second ends of a DNA fragment, first and second regions of complementarity that are subsequently hybridized with primers containing a promoter containing sequence and terminator containing sequence, respectively.

However, Shi fails to teach such a method. Looking at Figure 1 of Shi, (p. 49), it is clear

that to the extent a promoter containing primer contains a region that is complementary to a first region of complementarity as added on the second DNA fragment, i.e. a product of a first PCR amplification step, the terminator containing primer does not contain a region of complementarity that hybridizes to the second DNA fragment. In fact, as shown in Figure 1, the promoter containing sequence of Shi hybridizes to a first upstream target sequence while the terminator containing sequence (primer 10 (BSH)) that contains the "*Bam*HI cloning sites, and a pair of translational stop codons" does not contain a sequence that hybridizes to the same target sequence as that of the promoter containing sequence. Indeed, the BSH primer is used as the final primer in the amplification reaction (quoting page 49, first column of Shi).

To summarize, the claims require that the promoter containing sequence and terminator sequence hybridize to first and second regions of complementarity, respectively, that were added to a target sequence. The method in Shi fails to teach such a method because the promoter containing primer (if such a primer is even disclosed in Shi) and the terminator containing primer do not contain regions of complementarity that would hybridize to regions of complementarity that were added to the same initial target DNA.

The claim further requires joining the promoter-containing sequence to said *first end of said second DNA fragment* and said terminator-containing sequence to said *second end of said second DNA fragment* to form said third DNA fragment. Again, such a method is not disclosed in Shi because the promoter containing primer and terminator containing primer are not joined to first and second ends of the same DNA fragment.

For these reasons, Applicants respectfully request the Examiner to withdraw the rejection of claim 1 and those claims that depend from claim 1.

Claim 21, as amended, also requires contacting an intermediate nucleic acid fragment with third and fourth nucleic acid fragments that respectively comprise a region complementary to the first and second extension regions wherein each of the third and fourth fragments further comprise at least one nucleic acid region that confers function. In contrast, as noted above, Shi fails to teach such a method. In the method of Shi, only promoter sequence is added to an

upstream target nucleic acid, while translation terminator sequences are added to a distinct (the downstream fragment) target nucleic acid. Shi fails to disclose contacting a nucleic acid fragment with nucleic acid fragments that comprise regions complementary to first and second extension regions on the intermediate fragment, wherein each of the fragments comprise at least one nucleic acid region that confers function.

Likewise, claim 30 is directed to a system for adding a nucleic acid fragment that confers function to a polynucleotide target sequence. The system requires, *inter alia*, a 5' biological function conferring nucleic acid fragment *and* a 3' biological function conferring nucleic acid fragment. Each of the fragments comprises a region of complementarity to one of the extension regions of the extension primer pairs. One of the extension primers comprises a region of complementarity to a 5' strand of the polynucleotide target sequence and one of the extension primers comprises a region of complementarity to a 3' strand of the polynucleotide target sequence.

However, as noted previously, Shi fails to disclose such a method or system. Shi fails to teach primer pairs that include a 5' biological function conferring nucleic acid fragment and a 3' biological function conferring nucleic acid fragment, wherein each of the primers in the pair include a region complementary to extension primers that each contain regions of complementarity to a target nucleic acid. In contrast, at best Shi discloses primers that may form a promoter and are attached to the upstream target nucleic acid sequence and a primer that contains terminator sequences that attaches 3' of a distinct, downstream target nucleic acid.

Accordingly, Shi fails to teach each element of the rejected claims. As such, Applicants respectfully request the Examiner to withdraw the rejection.

Rejection Under 35 U.S.C. § 103

Claims 3, 20, 23, and 35 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Shi, et al. (described above) and Felgner, et al., (U.S. Patent No. 6,165,720). Applicants

respectfully traverse the rejection. In addition, Applicants note that claim 20 is canceled, without prejudice, herein. As such, the rejection of claim 20 is moot.

Shi, et al. is described above. Felgner, et al. discloses construction of nucleic acid vectors containing a PNA-binding site. Thus, according to the Examiner, the combination of the references renders claims 3, 20, 23, and 35 unpatentable.

The Applicants respectfully submit that the Examiner has failed to make out a *prima facie* case of obviousness. The legal concept of *prima facie* obviousness allocates who has the burden of going forward with production of evidence in each step of the examination process as between the PTO and the applicants. *See In re Rinehart*, 531 F.2d 1048, 189 U.S.P.Q. 143 (C.C.P.A. 1976); M.P.E.P. § 2142. It provides that the Examiner bears the initial burden of factually supporting any *prima facie* conclusion of obviousness. M.P.E.P. § 2142; *See also In re Piasecki*, 745 F.2d 1468, 1472, 223 U.S.P.Q. 785, 787 (Fed. Cir. 1984). If the Examiner does not make out a *prima facie* case of obviousness, the applicant is under no obligation to submit evidence of nonobviousness. M.P.E.P. § 2142.

In order to establish a *prima facie* case of obviousness, the PTO must satisfy three requirements. First, there must be some suggestion or motivation, either in the cited references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. *In re Fine*, 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988); M.P.E.P. § 2142; *Cf. Al-Site Corp. v. VSI Int'l Inc.*, 174 F.3d 1308, 50 U.S.P.Q.2d 1161 (Fed. Cir. 1999). Second, the proposed modification of the prior art must have a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. *Amgen, Inc. v. Chugai Pharmaceutical Co.*, 927 F.2d 1200, 1209, 18 U.S.P.Q. 1016, 1023 (Fed. Cir. 1991), *cert. denied*, 502 U.S. 856 (1991); *In re Erlich*, 22 U.S.P.Q. 1463, 1466 (Bd. Pat. App. & Int. 1992); *In re Dow Chem.*, 837 F.2d 469, 473, 5 U.S.P.Q.2d 1529, 1531. Third, the prior art reference (or references when combined) must teach or suggest all the claim limitations. *In re Wilson*, 424 F.2d 1382, 1385, 165 U.S.P.Q. 494, 496 (C.C.P.A. 1970); M.P.E.P. § 2142.

Here, Applicants submit that the combination of references fail to disclose each element

of the claims. Specifically, as noted above in the response to the 102 rejection, Shi fails to disclose that the promoter containing sequence and terminator sequence hybridize to first and second regions of complementarity, respectively, that were added to *a target sequence*. The method in Shi fails to teach such a method because the promoter containing primer (if such a primer is even disclosed in Shi) and the terminator containing primer do not contain regions of complementarity that would hybridize to regions of complementarity that were added to the *same* initial target DNA.

Moreover, Felgner does not provide any disclosure that would cure the defect of Shi et al. That is, as noted by the Examiner, Felgner discloses construction of nucleic acid vectors (or plasmids) containing PNA-binding sites. However, such a disclosure fails to cure the deficiencies of Shi et al. Accordingly, Applicants submit that the claims are not rendered obvious in light of the references taken individually or when combined because the combination of references fails to teach each element of the rejected claims. Applicants respectfully request the Examiner to withdraw the rejection.

Claims 7, 8, 17, 18, 24, 25, 36 and 37 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Shi, et al. (cited above) and Uhlman, et al. (U.S. Patent No. 6,063,571). Shi, et al. is described above. According to the Examiner, Uhlman et al. disclose amplification of nucleic acids with DNA/PNA primers. Thus, according to the Examiner, the combination of the references renders claims 7, 8, 17, 18, 24, 25, 36 and 37 unpatentable. Applicants respectfully traverse the rejection.

With respect to claims 17 and 18 the rejection is moot because the claims have been canceled, without prejudice, herein.

As noted above, Applicants submit that Shi fails to teach that the promoter containing sequence and terminator sequence hybridize to first and second regions of complementarity, respectively, that were added to a target sequence. The method in Shi fails to teach such a method because any putative promoter containing primer of Shi and the terminator containing primer do not contain regions of complementarity that would hybridize to regions of

complementarity that were added to the *same* initial target DNA.

Moreover, Uhlman does not provide any disclosure that would cure the defect of Shi et al. As the Examiner noted, Uhlman discloses amplification of nucleic acids with DNA/PNA primers, but this disclosure fails to cure the deficiencies of Shi et al. Accordingly, Applicant submit that the claims are not rendered obvious in light of the references taken individually or when combined because the combination of references fails to teach each element of the rejected claims. Applicants respectfully request the Examiner to withdraw the rejection.

Claims 7, 9, 17 and 19 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Shi, et al. (cited above) and Goodchild (Bioconjugate Chemistry, Vol. 1, pp. 165-187, 1990). With respect to claims 9 and 19, Applicants submit that the rejection is moot because claims 9 and 19 have been canceled, without prejudice, herein. Applicants respectfully traverse the rejection of the remaining claim.

As noted previously, Applicants submit that Shi fails to disclose that the promoter containing sequence and terminator sequence hybridize to first and second regions of complementarity, respectively, that were added to a target sequence. The method in Shi fails to teach such a method because any putative promoter containing primer of Shi and the terminator containing primer do not contain regions of complementarity that would hybridize to regions of complementarity that were added to the *same* initial target DNA.

Moreover, Goodchild does not provide any disclosure that would cure the defect of Shi et al. While Goodchild may disclose oligonucleotides modified with phosphorothioates, Applicants note that such a disclosure fails to cure the deficiencies of Shi et al. Accordingly, Applicants submit that the claims are not rendered obvious in light of the references taken individually or when combined because the combination of references fails to teach each element of the rejected claims. Applicants respectfully request the Examiner to withdraw the rejection.

Claims 38-41 and 43 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Shi, et al. (cited above) and Mullis, et al. (U.S. Patent No. 4965188). With respect to claim 40,

Applicants submit that the rejection is moot because the claim is canceled, without prejudice, herein. Applicants respectfully traverse the remaining rejections.

Shi, et al. is described above. According to the Examiner, Mullis discloses polymerase chain reaction (PCR) such that more than one target nucleic acid can be amplified using primers specific for its target.

However, as noted previously, Shi fails to disclose that the promoter containing sequence and terminator sequence hybridize to first and second regions of complementarity, respectively, that were added to a target sequence. The method in Shi fails to teach such a method because any putative promoter containing primer of Shi and the terminator containing primer do not contain regions of complementarity that would hybridize to regions of complementarity that were added to the *same* initial target DNA. Moreover, Applicants submit that while Mullis discloses a PCR method, there is no disclosure in Mullis that cures the deficiency of Shi et al.

In addition, Applicants note that the claim 38 recites the step of "creating extension primer pairs for each of a plurality of different target polypeptide-encoding sequences, each extension primer pair comprising first and second extension primers, respectively comprising first and second extension regions and a region of complementarity to a particular target sequence, such that the first and second extension regions for each extension primer pair are the same as the first and second extension regions for the other of said extension primer pairs, but the regions of complementarity are customized for each target sequence".

However, Applicants submit that neither Shi, nor Mullis, nor the combination of the references teaches such a step. That is, Shi fails to disclose amplification of multiple target nucleic acids with primers that contain the same 5' extension regions and regions of complementarity that are customized to a particular target sequence. In addition, Mullis fails to teach such a method. While it is true that Mullis discloses that the primers may have sequences non-complementary to the target attached at the 5' ends of the primers, this in no way teaches or suggests that the 5' ends of the primers contain the same 5' extension regions among all of the primers.

For all of the above reasons, Applicants submit that the references individually or in combination fail to teach each element of the claims. Applicants respectfully request the Examiner to withdraw the rejection.

Claims 44 and 45 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Shi, et al. (cited above) and Uhlman, et al. (U.S. Patent No. 6,063,571).

Claim 44, as amended, recites, *inter alia*, that each of the third and fourth nucleic acid fragments comprises a nucleic acid region that confers function. Also, following a second PCR amplification reaction, the first and second functional nucleic acid regions are joined to the polynucleotide target sequence.

However, as noted previously, Shi fail to disclose such a method wherein first and second functional sequences are attached to the same target nucleic acid. Moreover, as noted previously, while Uhlman discloses amplification with DNA/PNA primers this in no way cures the deficiency of Shi et al, as described above.

Accordingly, Applicants submit that the rejection in light of Shi and Uhlman has been overcome. Applicants respectfully request the Examiner to withdraw the rejection.

CONCLUSION

In conclusion, the present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited. Should there be any further issues outstanding, the Examiner is invited to contact the undersigned attorney at the telephone number shown below.

Applicants will be submitting a new Power of Attorney in the instant case. Until then, this Response is submitted in compliance with 37 C.F.R. 1.34.

Please charge any additional fees, including fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641** (referencing Attorney's Docket No. **40019-0004**).

Respectfully submitted,

Date: April 29, 2005

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